Best Practice

STRAIGHT TO THE POINT

Dyspepsia, peptic ulcer disease, and esophageal reflux disease

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EPIDEMIOLOGY

Dyspepsia

Dyspepsia is defined as episodic or persistent pain or discomfort localized to the upper abdomen.

- The constellation of symptoms may include gas, bloating, nausea, vomiting, and early satiety
- Twenty-six percent of the adult population complains of dyspepsia each year, and 10% experiences heartburn daily[1]
- In 1997, there were 18,785,000 ambulatory care visits in the United States for stomach and abdominal pain, cramps, and spasms. Dyspepsia was the third most common symptomatic reason for visiting an ambulatory care setting[2]

[1] *Talley NJ, Zinsmeister AR, Schleck CD, Melton LJ 3rd. Dyspepsia and dyspepsia subgroups: a population-based study. Gastroenterology 1992;102(pt 1):1259-1268.* A representative sample of 835 adults living in Olmsted County, Minnesota.

[2] *Ambulatory Care Visits to Physician Offices, Hospital Outpatient Departments, and Emergency Departments: United States, 1997. Data from the National Health Care Survey. Hyattsville, MD: National Center for Health Statistics; 1997.*

Peptic ulcer disease

- The US prevalence of peptic ulcer disease (PUD) is 1%, and the lifetime cumulative incidence is 10% for men and 4% for women. The prevalence and incidence of PUD have declined for the past 2 decades, probably because of decreasing rates of *Helicobacter pylori* infection
- A total of 400,000 new cases of PUD are diagnosed each year
- Duodenal ulcers are twice as common in men as in women and 1.5 times as common as gastric ulcers
- Peak incidence is in the 40s for men and in the 50s to 60s for women

PUD as a chronic disease

- As much as 90% of patients with duodenal ulcers will have a recurrence (many asymptomatic) within 1 year if not given maintenance therapy and if *H pylori* is not eradicated[3]
- Risk factors for PUD beyond *H pylori* infection include use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), male sex, family history, stress, smoking, chronic renal failure, chronic obstructive pulmonary disease, and alcoholism

[3] *Soll AH. Consensus conference: medical treatment of peptic ulcer disease: practice guidelines. Practice Parameters Committee of the American College of Gastroenterology. JAMA 1996;275:622-629.* Complications of PUD include bleeding or perforation in 1% to 3% per year. One to three percent of gastric ulcers coincide with gastric carcinoma.

Helicobacter pylori

- *H pylori* is a gram-negative, urease-producing bacterium that colonizes gastric mucosa and produces chronic, superficial antral gastritis
- One of the world's most common bacterial pathogens, its prevalence in the general US population is 40% and 70% to 80% in the developing world[4]
- Prevalence is 50% by age 50 years and is highest among African and Latino Americans
- Its incidence in the developed world has decreased markedly with improved sanitary conditions, with new infection rates now at less than 0.5% per year. Therefore, most current infections reflect exposure during childhood
- The consensus is that *H pylori* is the major cause of chronic gastritis and duodenal and gastric ulcers
- Koch's postulates have been met for gastritis, and the evidence is overwhelming for PUD
- More than 95% of patients with PUD are infected with *H pylori*
- For nonulcer dyspepsia, however, the prevalence of *H pylori* infection is no higher than that in the general population
- For gastric carcinoma, non-Hodgkin's lymphoma, and mucosa-associated lymphoid tissue (MALT) lymphoma, there is evidence of a strong association with *H pylori* infection
- Causal evidence is strongest for MALT lymphomas, some of which completely disappear with the eradication of *H pylori*[5]

[4] *NIH Consensus Conference. Helicobacter pylori in peptic ulcer disease. JAMA 1994; 272:65-69.* This important summary received considerable media attention and increased public awareness of *H pylori*.

Koch's postulates

- The microorganism in question must always be present in diseased hosts
- The microorganism must be isolated from the diseased host and grown in pure culture
- Microorganisms obtained from the pure culture, when injected into a healthy susceptible host, must produce the disease in that host
- Microorganisms must be isolated from the experimentally infected host, grown in pure culture, and compared with those in the original culture

[5] *Bayerdorffer E, Neubauer A, Rudolph B, et al. Regression of primary gastric lymphoma of mucosa-associated lymphoid tissue type after cure of* Helicobacter pylori *infection. MALT Lymphoma Study Group. Lancet 1995;345:1591-1594.* Cancer cured with antibiotics?!

Gastroesophageal reflux disease[6]

- Ten percent of the US population has daily heartburn
- Barrett's esophagus—replacement of the squamous epithelium of the esophagus by columnar epithelium—develops in 10% to 15% of patients who have chronic gastroesophageal reflux disease (GERD). Barrett's esophagus is associated with an increased risk of esophageal adenocarcinoma

[6] *DeVault KR, Castell DO, for the Practice Parameters Committee of the American College of Gastroenterology. Guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Arch Intern Med 1995;155:2165-2173.*

DIAGNOSIS

Nonulcer dyspepsia

- Nonulcer dyspepsia is a common clinical syndrome with varied presentation and a multifactorial etiology
- It is defined as chronic dyspeptic symptoms (episodic or persistent pain or discomfort localized to the epigastrium or upper abdomen), for which clinical evaluation and studies have failed to reveal a pathologic cause.[7] It is, therefore, a diagnosis of exclusion
- Patients can be grouped by symptom pattern as ulcerlike, dysmotility-like, and refluxlike, but there is much overlap
- Differential diagnoses include PUD (5%-30%), irritable bowel syndrome (23%), GERD (22%), and chronic biliary or pancreatic disorders (5%-10%)[8]

[7] *Talley NJ, Colin-Jones D, Koch KJ, Koch M, Nyrén O, Stanghellini V. Functional dyspepsia: a classification with guidelines for diagnosis and management. Gastroenterol Int 1991;4:145-160.* The Rome criteria for nonulcer dyspepsia.

[8] *Camilleri M. Nonulcer dyspepsia: a look into the future. Mayo Clin Proc 1996;71:614-622.* A good review of pathogenesis.

Peptic ulcer disease

- Diagnosing PUD by clinical evaluation alone is challenging
- Textbook descriptions of classic presentations have not been supported by evidence

- The best study to date found 4 independent clinical predictors[9]
- If any one of these findings is present, the decision rule has a sensitivity of 95%, specificity of 30%, a positive likelihood ratio (LR) of 1.4, and negative LR of 0.2
- The high sensitivity may help to rule out the diagnosis; in the absence of any of these findings, the probability of PUD drops from 10% (baseline prevalence) to 2% (probability after history)
- In a study of 659 patients who had upper gastrointestinal (GI) tract radiographic series (UGI) in an urban health center, the independent predictors of an abnormal radiographic finding were age older than 45 years, male sex, history of PUD, pain at night, and lack of bowel symptoms[10]
- Physical examination is most helpful in exploring nonpeptic acid disorders in the differential diagnosis. Localized epigastric tenderness is common and nonspecific. Examination of stool for occult bleeding is important to guide prognosis and further diagnostic investigation
- The two studies for diagnosing PUD are double-contrast UGI and esophagogastroduodenoscopy (EGD)
- The higher sensitivity of EGD[11] makes it a better test to rule out PUD, but the difference is not as large as it at first appears. If the pretest probability is 10%, then the posttest probability is 1.5% after a normal UGI and 0.5% after a normal EGD
- The choice of test is often dictated by availability

Helicobacter pylori

There are five methods for diagnosing *H pylori* infection[12]

- The serologic test is an enzyme-linked immunosorbent assay for IgG antibodies to *H pylori*. Like most serologic tests, it cannot distinguish between active infection and serologic scar. A quick, inexpensive, office-based qualitative test for *H pylori* antibodies is also available
- The urea breath test is based on the ingestion of carbon-labeled urea, which is hydrolyzed by *H pylori* urease to labeled bicarbonate and exhaled as labeled carbon dioxide, which can be measured. This test is quick, inexpensive, and highly accurate—the ideal test for the presence and eradication of *H pylori*
- The invasive tests all require EGD and are, therefore, more expensive. The rapid urease test is a rapid, pH-based, urease biopsy test. False-negative results occur because of biopsy sampling errors. For patients requiring EGD, the rapid urease test is the preferred test
- Histologic examination is highly sensitive and allows examination of the mucosa. It is reasonable to obtain specimens for histologic examination only if the rapid urease test is negative
- Culture is insensitive because the organism is fastidious. It should be used only when antibiotic sensitivities are needed

GERD

- Heartburn (tight, burning sensation radiating from the xiphoid process to the neck) and acid regurgitation are typical symptoms[13]
- Symptoms are exacerbated by fatty foods, caffeine, and recumbent position
- GERD can mimic or exacerbate other diseases. Hoarseness, chronic cough, dental erosions, and asthma exacerbation may all occur with or without typical symptoms of GERD. Heartburn can mimic atypical angina

[9] *Marton KI, Sox HC Jr, Wasson J, Duisenberg CE. The clinical value of the upper gastrointestinal tract roentgenogram series. Arch Intern Med 1980;140:191-195.* This well-done diagnostic study in 483 Veterans Affairs outpatients identified the following predictors:

Clinical predictors of PUD	LR+
History of duodenal ulcer	3.9
Age >50 yr	1.5
Pain decreased by taking food or milk	1.7
Pain usually occurs soon after meals	1.4

LR+ = likelihood ratio of PUD being present ("positive").

[10] *Schwartz MD, Lee E, Lipkin M, Yedidia MJ. Dyspepsia in the inner city: predictors of an abnormal UGI. J Gen Intern Med 1997;12(suppl):57.* In this study at Gouverneur Diagnostic and Treatment Center in New York City, about 90% of patients had normal or unimportant findings on UGI. If the test-no test threshold is much below 10%, then it is prudent to evaluate most dyspeptic patients with UGI or esophagogastroduodenoscopy.

[11] *Dooley CP, Larson AW, Stace NH, et al. Double-contrast barium meal and upper gastrointestinal endoscopy: a comparative study. Ann Intern Med 1984;101:538-545.*

Operating characteristics of UGI and EGD[11]

Characteristics	UGI	EGD
Sensitivity, %	85	95
Specificity, %	95	99
Positive LR	17	95
Negative LR	0.16	0.05

[12] *Cave DR, Hoffman JS. Management of* Helicobacter pylori *infection in ulcer disease. Hosp Pract 1996:63-64, 67-69, 73-75.*

Efficacy and relative cost of 5 methods of diagnosing H pylori *infection*

Test	Sensitivity, %	Specificity, %	Cost
Serologic	95	86–95	$
Breath test	90–95	98–100	$$
Rapid urease	90–95	90–98	$$$
Histologic	93–99	95–99	$$$$
Culture	70–95	100	$$$$

[13] *Klauser AG, Schindlbeck NE, Müller-Lissner SA. Symptoms in gastro-oesophageal reflux disease. Lancet 1990;335:205-208.*

Diagnostic testing

- In the approach to patients with heartburn but without alarm symptoms, a reasonable first step is an empiric trial of a proton pump inhibitor (PPI). In one study, high doses of omeprazole (40 mg twice a day for 7 days) were used as a diagnostic test.[14] The relief of symptoms by 75% counted as a positive result and was 83% sensitive for GERD. Further diagnostic testing should be considered in patients who do not respond to an empiric trial
- Barium radiography has varying sensitivity, depending on the severity of disease, and shows abnormalities in 20% of patients without disease (80% specific)
- On upper GI tract endoscopy, only 25% of patients with GERD have macroscopic changes of esophagitis by visual inspection, and only 50% have esophagitis on examination of a biopsy specimen. Because of the risk of Barrett's esophagus, endoscopy should be considered in patients with severe or treatment-resistant disease

Accuracy of typical symptoms in diagnosis of GERD

Variable	Sensitivity, %	Specificity, %
Symptom present		
Acid regurgitation	60	52
Heartburn	68	52
Retrosternal burning	61	51
Dominant symptom		
Acid regurgitation	6	95
Heartburn	38	89
Retrosternal burning	14	84

[14] *Schindlbeck NE, Klauser AG, Voderholzer WA, Müller-Lissner SA. Empiric therapy for gastroesophageal reflux disease. Arch Intern Med 1995;155:1808-1812.* The sensitivity of this test was 83% with omeprazole, 40 mg twice a day, and only 27% with omeprazole, 40 mg daily.

TREATMENT

Nonulcer dyspepsia

Two recent practice guidelines suggest the following approach to a patient with undiagnosed dyspepsia[15,16]

- First, consider other causes, including cardiac, hepatobiliary, and medication-induced. If present, treat the other cause
- If there is no other apparent cause, assess whether the patient is aged 50 years or older or alarm features are present. Alarm features—vomiting, bleeding or anemia, unexplained weight loss, abdominal mass, and dysphagia—are indications for prompt EGD
- If the patient is younger than 50 years and without alarm features, evaluate for aspirin or NSAID use. Discontinue aspirin or any NSAIDs or switch to acetaminophen or a cyclo-oxygenase type 2 inhibitor and reassess the patient
- If no aspirin or NSAIDs are being used, assess whether the predominant symptom is heartburn (a rising burning sensation) or regurgitation. If yes for either, treat as GERD with a PPI or histamine-2 (H_2)-receptor blocker for 4 weeks and reassess the patient. Investigate with EGD if reflux symptoms persist or recur
- If the predominant symptom is not heartburn or regurgitation, consider one of the following three strategies: empiric antiulcer treatment, evaluation with UGI or EGD, or test and treat for *H pylori* infection

[15] *Veldhuyzen van Zanten SJO, Flook N, Chiba N, et al. An evidence-based approach to the management of uninvestigated dyspepsia in the era of* Helicobacter pylori. *Canadian Dyspepsia Working Group. CMAJ 2000;162(suppl 12):S3-S23.*

[16] *Howden CW, Hunt RH. Guidelines for the management of* Helicobacter pylori *infection. Am J Gastroenterol 1998;93:2330-2338.*

Empiric antiulcer treatment

- A 4- to 6-week trial of therapy with antacids or an H_2-receptor antagonist
- If symptoms do not respond in 2 to 4 weeks, or if symptoms recur after treatment is stopped at 6 weeks, further workup should be done

Of the three strategies for nonulcer dyspepsia, the best approach is still unclear. Testing and treating *H pylori* is initially the most cost-effective, but because many patients ultimately need further evaluation, UGI or EGD has been shown to be most cost-effective over the long term.[17] Empiric antiulcer treatment is a rational approach unless the patient is at high risk, as defined earlier.

[17] *Bytzer P, Hansen JM, Schaffalitzky de Muckadell OB. Empirical H_2-blocker therapy or prompt endoscopy in management of dyspepsia. Lancet 1994;343:811-816.* A randomized controlled trial of 414 patients showed that those randomly allocated to prompt EGDs were more satisfied, had lower health care costs, and had fewer sick-leave days than patients treated empirically.

Evaluation with UGI or EGD

- Advised in higher risk patients—those aged 50 years or older or those with the predictive diagnostic features noted earlier

Noninvasive testing for *H pylori* and antibiotics for infected patients ("test-and-treat" strategy)

- Only 15% to 30% of patients with dyspepsia who are infected with *H pylori* have PUD

- Eradication of *H pylori* in patients with nonulcer dyspepsia (the other 70%-85%) has not been shown to be more effective than placebo in lessening symptoms in randomized trials

Empiric antibiotic treatment of all patients without *H pylori* testing is strongly discouraged. Antibiotics are of no use in uninfected patients, and widespread antibiotic use may lead to resistance and adverse effects.

Active ulcers

- All four major options for the treatment of active gastric and duodenal ulcers have comparable healing rates. H_2-receptor blockers, PPIs, high-dose antacids, and sucralfate all heal more than 90% of ulcers within 4 to 6 weeks (see Table on our web site linked to this article)
- PPIs induce more rapid healing than H_2-receptor blockers[18]
- Concomitant eradication of *H pylori* facilitates ulcer healing and decreases recurrence[19]
- Treatment is generally given for 6 weeks for duodenal ulcers and 8 weeks for gastric ulcers
- Persistent symptoms should prompt a search for NSAID or aspirin use, in which the differential diagnosis is reviewed and EGD performed. (UGI is not adequate to assess ulcer healing)[4]
- Follow-up EGD is generally indicated for gastric ulcers to assess healing and exclude the possibility of carcinoma

[18] *Maton PN. Omeprazole. N Engl J Med 1991;324:965-975.*

[19] *Graham DY, Lew GM, Evans DG, Evans DJ Jr, Klein PD. Effect of triple therapy (antibiotics plus bismuth) on duodenal ulcer healing: a randomized controlled trial. Ann Intern Med 1991;115:266-269.* The first randomized controlled trial to show that PUD heals faster with the addition of antibiotics for *H pylori*.

H pylori eradication

Treatment regimens

Regimens with the highest eradication rates:

- For 2 weeks, a PPI twice a day; clarithromycin, 500 mg twice a day; and amoxicillin, 1 g twice a day (or metronidazole, 500 mg twice a day if patient is allergic to penicillin)
- For 2 weeks, ranitidine; bismuth citrate, 400 mg twice a day; clarithromycin, 500 mg twice a day; and amoxicillin, 1 g twice a day (or metronidazole, 500 mg twice a day if patient is allergic to penicillin)
- For 2 weeks, a PPI twice a day; bismuth subsalicylate, 2 tablets 4 times a day; metronidazole, 250 mg 4 times a day; and tetracycline hydrochloride, 250 mg 4 times a day
- In summary, all patients with PUD who are infected with *H pylori* (>95%) should be treated with one of these regimens. The choice of regimen depends on predicted compliance, cost, and availability

This is a rapidly evolving field. Next year's regimens will likely be easier to prescribe and to take without sacrificing efficacy.

Prevention of ulcer recurrence

- For most patients with PUD, by eradicating *H pylori,* we can now cure a previously chronic, recurrent disorder. Eradicating *H pylori* infection dramatically and consistently decreases the rate of ulcer recurrence[20]

Consensus about the need for subsequent treatment with H_2-receptor blockers is evolving, but at this point patients should receive the usual 6- to 8-week course of ulcer healing therapy following antimicrobial treatment. This is especially the case for large, complicated, refractory, or gastric ulcers.

[20] *Walsh JH, Petterson WL. The treatment of* Helicobacter pylori *infection in the management of peptic ulcer disease. N Engl J Med 1995;333:984-991.*

Which patients infected with *H pylori* should be treated with antibiotics?

- Definitely treat patients who have duodenal ulcer, gastric ulcer, or MALT lymphoma
- Possibly treat patients who have a high risk of gastric cancer, a gastric cancer precursor lesion, or persistent nonulcer dyspepsia who insist on treatment
- Do not treat patients who have no symptoms or have GERD

- This is a powerful intervention. A National Institutes of Health consensus panel concluded that all ulcer patients with *H pylori* infection require treatment with antimicrobial agents in addition to antisecretory drugs, whether on first presentation or recurrence[4]

The 1-year recurrence rate for PUD typically drops from about 85% to 10% with eradication (relative risk ratio = 88%; number needed to treat = 1.3). 77 ulcer recurrences are prevented for every 100 patients treated with antibiotics.[21]

[21] *Hentschel E, Brandstatter G, Dragosics B, et al. Effect of ranitidine and amoxicillin plus metronidazole in the eradication of* Helicobacter pylori *and the recurrence of duodenal ulcer. N Engl J Med 1993;328:308-312.*

GERD

- Treatments include PPIs, H_2-receptor antagonists, and prokinetic agents. PPIs are clearly superior to other agents

Empiric treatment of GERD: odds ratios (OR) of outcomes for different agents[22]

Drug	OR of remitting	OR of improving
H_2-receptor blocker vs placebo	1.8*	2.6*
Prokinetic vs placebo	1.5	1.7*
PPI vs H_2 receptor blocker	2.2*	1.7*
PPI vs prokinetic	2.2*	†

*$P < 0.05$.
†In this meta-analysis, an insufficient number of trials of PPI vs prokinetics report the same outcomes for improving symptoms.

[22] *van Pinxteren B, Numans B, Bonis PA, Lau J. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Library: Cochrane Database of Systematic Reviews. Issue 4. Oxford, UK: Update Software; 2000.* Meta-analyses of 6,607 patients in 21 randomized controlled trials.

Efficacy of PPIs versus H_2-receptor blockers for GERD

Drug regimen	Patients asymptomatic after 14 days of continuous therapy, %*
Ranitidine, 150 mg twice a day	26
Omeprazole, 10 mg a day	40
Omeprazole, 20 mg a day	55

*From Bardhan et al.[23]

[23] *Bardhan KD, Müller-Lissner S, Bigard MA, et al. Symptomatic gastro-oesophageal reflux disease: double blind controlled study of intermittent treatment with omeprazole or ranitidine. The European Study Group. BMJ 1999;318:502-507.* A large well-designed study.

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We are grateful for the support of this group of experts. We are lucky to have them.